

✓ OPTIMIZATION OF A BIOCHEMICAL FED-BATCH REACTOR USING PULSE FEEDS

A Thesis Submitted
in Partial Fulfillment of the Requirements
for the Degree of
MASTER OF TECHNOLOGY

by
V.C . LAKSHMI NARAYANA MURTHY

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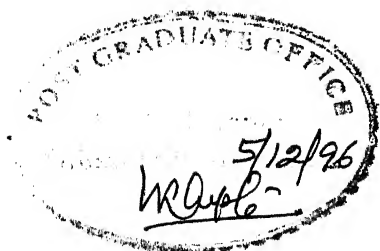
Certified that the work contained in the thesis entitled "Optimization of a Biochemical Fed-Batch Reactor Using Pulse Feeds", by V.C.L.N. Murthy, has been carried out under my supervision and that this work has not been submitted elsewhere for a degree.



(Dr. S. Pushpavanam)

Department of Chemical Engineering
Indian Institute of Technology
Kanpur

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V.C.L.N. Murthy

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Nomenclature

F	:	Volumetric flow-rate (L/hr)
K_m, K_i	:	Haldane kinetic parameters
N	:	No. of stages
r	:	Ratio of two successive volumes of the reactor
S	:	Substrate concentration (g/L)
S_F	:	Feed substrate concentration (g/L)
S_O	:	Initial substrate concentration (g/L)
S^*	:	The substrate concentration at which the reaction rate is a maximum
t	:	Time (hr)
t_f	:	Final time (hr)
Δt	:	Duration of sub-interval (hr)
u	:	Biomass concentration immediately after the addition of each pulse
V	:	Volume of the reactor (L)
V_O	:	Initial volume of the reactor (L)
V_f	:	Final volume of the reactor (L)
ΔV	:	Volume of pulse (L)
X	:	Biomass concentration (g/L)
X_O	:	Initial biomass concentration (g/L)
X_f	:	Final biomass concentration (g/L)
Y	:	Constant yield

Greek:

μ	:	Specific growth rate (hr^{-1})
μ_m	:	Specific growth rate constant

Subscripts:

o : Initial
f : Final
F : Feed
i : i^{th} stage

Superscripts:

- : At the end of each sub-interval
+ : After the addition of the pulse, or at the beginning of a sub interval.
* : maximum

Abstract

In this work we analyse the optimal control problem of a biochemical reactor sustaining a reaction characterised by substrate inhibition. The control variable is the substrate feed rate. We approximate the feed rate policy by discrete pulses. The entire period of operation is divided into sub-intervals. The substrate is assumed to be added at the ~~end~~^{beginning} of each sub-interval as pulses.

The optimisation problem is solved analytically when the initial condition is stoichiometric. A sequential quadratic programming is used to determine the optimal policy when the initial condition is non-stoichiometric. We consider two cases i) when all sub-intervals are of equal duration ii) when the optimum duration of each sub-interval has to be found. The effect of initial conditions on the optimal profile is also investigated. We consider four possible modes of the operation of the reactor when (i) the final volume is fixed, final time is fixed, (ii) the final volume is free, final time is fixed, (iii) the final volume is fixed, final time is free, (iv) the final volume is free, final time is free.

CHAPTER 1

INTRODUCTION

Bio-chemical reactions characterised by substrate inhibition exhibit an optimum performance when the reactor is operated in the fed-batch mode. Here the substrate is fed to the reactor over a period of time to ensure that the reaction rate is close to the maximum in the reactor (Cazzador (1988), San and Stephanopolous (1984)).

Pontryagin's (1977) maximum principle has been used to solve this optimal control problem. Since the control variable, the substrate feed-rate occurs linearly in the system, the optimal policy is bang-bang and/or follows a singular trajectory. The control variable is maintained at its upper or lower bound, in bang-bang control, while along the singular arc the control variable varies continuously between the lower and upper bound.

Cazzador (1988) has studied the optimal feed rate profiles for fed batch fermentation that maximises the biomass production and the effect of initial conditions.

Fishman and Biryukov (1974) considered the problem of optimal glucose feed strategy for pencilin production. However, they did not give a numerical scheme, and ignored volume changes arising from the addition of the feed.

Weigand et al. (1981) reduced the problem of optimal feed rate determination for single cell protein production to one in which the total time of operation is minimised for a fixed rate of biomass production. This was analysed for the repeated fed-batch operation.

Park and Rogers have experimentally studied the factors which influence the growth kinetics of the L-phenylalanine strain of E-coli NST74. From the batch culture data it was observed that the increased initial glucose levels and increased L-phenylalanine product concentration caused a decrease in the specific rates of growth and rate of product formation, thereby reducing the yields. In fed-batch culture a relatively high L-phenylalanine concentration was achieved.

The application of the continuous maximum principle though elegant possesses many numerical problems. For problems linear in the control variable, the control action is divided into several parts - when the variable is at its upper bound, when it is at its lower bound or when it varies continuously. The convergence of the numerical scheme usually needs a priori information about the exact sequence of the different control actions. This is usually obtained using information from the physics of the problem (Modak (1986)).

In many problems however the interactions between the different variables can be very complex. Under these conditions it is not possible to decide on the exact sequence of control profiles which results in optimal performance. It is also experimentally difficult to maintain an optimal profile which varies continuously. In bio-chemical systems this problem is often avoided by adding the substrate as pulses at discrete instants of time.

Sargent et al. (1984) used a Sequential Quadratic Programming approach to determine the optimum feeding policy of a reactant in a series-parallel reaction sequence. They divided the entire

duration into different stages and obtained the flow rates required for optimum performance in each stage.

Biegler et al. (1984) have developed a technique based on Sequential Quadratic Programming and orthogonal collocation which enables us to evaluate the optimal variable efficiently.

Rosen and Luus (1991) have discussed the methods for calculating gradients for nonlinear optimal control problems for the rapid convergence.

In this work we discuss the approximation of the optimal policy by discretising the substrate-feed rate with pulses. The substrate is assumed to be added at discrete points of time. The reaction is assumed to have a Haldane dependency on the substrate concentration. When the initial conditions of the reactor are stoichiometric, the order of the equations can be reduced by one and this permits an analytical solution. For the case when the initial state is non-stoichiometric the system of equations has to be solved simultaneously. Here we have used a Sequential Quadratic Programming technique to obtain the pulse feed-rate policy for different number of sub-intervals.

The effect of the initial state of the reactor is determined for both these cases. The optimal operation is discussed for (i) the final volume is fixed, final time is fixed, (ii) the final volume is free, final time is fixed, (iii) the final volume is fixed, final time is free, (iv) the final volume is free, final time is free.

CHAPTER 2

Problem Formulation and Method of Solution

In our mode of operation the substrate is added instantaneously at discrete points of time. These time instants signal the beginning of each sub-interval. The entire cycle of reactor operation here is divided into different sub-intervals. In each sub-interval the reactor is operated in batch mode. The pulses which are added at the beginning of a sub-interval change the initial conditions for that sub-interval.

The entire time of operation $[t_o, t_f]$ is divided into N different sub-intervals. The evolution in the i^{th} sub-interval ($t_{i-1} < t < t_i$) is governed by, the equations of the batch reactor

$$\dot{X} = \mu(S) \cdot X \quad 1(a)$$

$$\dot{S} = - \frac{\mu(S)}{Y} \cdot X \quad 1(b)$$

The equations represent the reactor state before the addition of the pulse at t_i . Here X and S represent the concentration of cell mass and substrate respectively and V is the volume of the reactor in the i^{th} interval and $\mu(S)$ is specific rate of growth.

These evolution of the system is subject to initial condition. These conditions specify the state at the beginning i.e. t_o^- , or before the addition of the pulse at t_o^- as

$$X(t_o^-) = X_o \quad 2(a)$$

$$S(t_o^-) = S_o \quad 2(b)$$

$$V(t_o^-) = V_o \quad 2(c)$$

For the numerical work a substrate inhibition model is taken from the literature. The dependency of the specific growth rate on S

is assumed to be given by

$$\mu(S) = \frac{\mu_m}{1 + \frac{Km}{S} + \frac{S}{K_i}}$$

From the mass balance equations at the time instants when the pulses are added, we have,

$$X(t_{i-1}^+) = \frac{V_{i-1}}{V_i} X(t_{i-1}^-) \quad 3(a)$$

$$S(t_{i-1}^+) = \frac{V_{i-1}}{V_i} S(t_{i-1}^-) + \frac{V_i - V_{i-1}}{V_i} S_F \quad 3(b)$$

where the subscript F stands for feed conditions. Here t_i^+ , t_i^- represent the instants immediately after and just before the addition of the pulse at $t = t_i$. The pulse is assumed to contain only substrate and no biomass. Our objective is to seek the pulses ΔV_i 's to be added at t_i 's which will maximise the biomass concentration $X(t_f)$. A schematic indicating the different variables is depicted in Fig. 1.

Methods of Solution:

We solve this problem using two techniques

- (i) Integral method
- (ii) Sequential Quadratic Programming (SQP)

(i) Integral Method: This technique can be used only when the initial conditions are in stoichiometric. The initial conditions are said to be stoichiometric when they satisfy

$$\frac{X(t_0^-)}{Y} + S(t_0^-) = S_F \quad 4(a)$$

After the addition of the first pulse (ΔV_1) the volume becomes

$$V_1 = V_0 + \Delta V_1 \quad 5(a)$$

The biomass and substrate concentrations after the pulse addition,

i.e., at t_0^+ , are

$$X(t_0^+) = \frac{V_0}{V_1} X(t_0^-) \quad 5(b)$$

$$S(t_0^+) = \frac{V_0}{V_1} S(t_0^-) + \frac{V_1 - V_0}{V_1} S_F \quad 5(c)$$

Adding the two equations 5(b-c) we obtain

$$\begin{aligned} \frac{X(t_0^+)}{Y} + S(t_0^+) &= \frac{V_0}{V_1} \left[\frac{X(t_0^-)}{Y} + S(t_0^-) \right] + S_F - \frac{V_0}{V_1} S_F \\ &= S_F \end{aligned}$$

This last identity follows from 4(a).

The evolution of the system (1a-b) during the batch is such that

$$\frac{d}{dt} \left(\frac{X}{Y} + S \right) = 0 \quad 6(a)$$

$$\text{or } \frac{X(t)}{Y} + S(t) = S_F \quad \text{for } t_{i-1} < t < t_i \quad 6(b)$$

clearly

$$\frac{X(t_i^-)}{Y} + S(t_i^-) = S_F = \frac{X(t_{i-1}^-)}{Y} + S(t_{i-1}^-) \quad 6(c)$$

Hence the variables X , S satisfy the stoichiometric relation for all 't' when the initial conditions at t_0^- are stoichiometric. This can be used to eliminate S in favour of X as

$$S = g(X) = S_F - \frac{X}{Y} \quad (7)$$

Then equation 1(a) and 2(b) can be reduced to the single equation

$$\dot{X} = \mu(g(X))X \quad (8)$$

Integrating this from t_0^+ to t_1^- , we obtain

$$t = \int_{X(t_0^+)}^{X(t_1^-)} \frac{dX}{X\mu(g(X))} = t_1 - t_0 \quad 9(a)$$

Thus, the total final time of operation t_f we have

$$t_f = t_N - t_0 = \int_{X(t_0^+)}^{X(t_1^-)} \frac{dX}{X\mu(X)} + \int_{X(t_1^+)}^{X(t_2^-)} \frac{dX}{X\mu(X)} + \dots + \int_{X(t_{N-1}^+)}^{X(t_N^-)} \frac{dX}{X\mu(X)} \quad 9(b)$$

Using the jump discontinuity conditions 3(a,b) which arise due to the instantaneous pulses this yields

$$t_f = \int_{X(t_0^-)}^{X(t_1^+)} \frac{V_2}{V_1} \frac{dX}{X\mu(X)} + \int_{X(t_1^+)}^{X(t_2^+)} \frac{V_3}{V_2} \frac{dX}{X\mu(X)} \dots + \int_{X(t_{N-1}^+)}^{X_f} \frac{dX}{X\mu(X)} \quad (10)$$

The variables which are to be determined are (i) the volumes of the reactor, V_i , in each sub-interval i or alternatively the pulses to be added at t_i 's and (ii) the duration of each sub-interval. Alternatively we can evaluate the cell mass concentration at the end of each sub-interval, $X(t_i^-)$, instead of the duration of each sub-interval, since these uniquely determine the duration of each sub-interval. In the first part of the work we consider our manipulated variables to be $X(t_i^+)$ and V_i 's

Our objective is to maximise the biomass concentration at the end of the cycle i.e., $X(t_f)$ or X_f . The subscript f is used to denote the final state of the reactor. The total number of variables to be determined are $2N$. These are N , Δt_i 's, and N , ΔV_i 's

At the optimum conditions

$$\frac{\partial X_f}{\partial X(t_i^+)} = 0 \quad \text{for } i = 0 \quad 11(a)$$

$$\text{and } \frac{\partial X_f}{\partial V_i} = 0 \quad 11(b)$$

using these on (10) yields

$$\mu(X(t_i^+)) = \mu\left(X(t_i^+) \frac{V_{i+1}}{V_i}\right) \quad \text{for } i = 1, 2, \dots, (N-1) \quad 12(a)$$

$$\mu\left(\frac{X_o V_o}{V_1}\right) = \mu\left(X(t_i^+) \frac{V_{i+1}}{V_i}\right) = \mu\left(X(t_{i+1}^+) \frac{V_{i+2}}{V_{i+1}}\right) \quad \text{for } i = 1, 2, \dots, (N-2) \quad 12(b)$$

Combining both (12a-b)

$$\mu\left(\frac{X_o V_o}{V_1}\right) = \mu(X(t_i^+)) = \mu\left(X(t_i^+) \frac{V_{i+1}}{V_i}\right) = \mu\left(X(t_{i+1}^+) \frac{V_{i+2}}{V_{i+1}}\right) \quad 12(c)$$

for $1 \leq i \leq N-1$

Writing it out for each, i

$$\mu(X(t_1^+)) = \mu(X(t_2^+)) = \dots = \mu(X(t_{N-1}^+)) = \mu(X(t_o^+)) \quad 13(a)$$

$$\mu\left(X(t_1^+) \frac{V_2}{V_1}\right) = \mu\left(X(t_2^+) \frac{V_3}{V_2}\right) = \dots = \mu\left(X(t_{N-1}^+) \frac{V_f}{V_{N-1}}\right) \quad 13(b)$$

$= \mu(X(t_o^+))$

the possible solutions are

$$X(t_1^+) = X(t_2^+) = \dots = X(t_{N-1}^+) = \frac{X_o V_o}{V_1} \quad 14(a)$$

$$X(t_1^+) \frac{V_2}{V_1} = X(t_2^+) \frac{V_3}{V_2} = \dots = \frac{X_o V_o}{V_1} \quad 14(b)$$

Since the form of kinetic equation is such that there can be at most two values of X , $X_1 (\neq X_2)$ for which

$$\mu(X_1) = \mu(X_2),$$

A possible solution is

$$\frac{V_2}{V_1} = \frac{V_3}{V_2} = \dots = \frac{V_f}{V_{N-1}} = r \quad 15(a)$$

$$\text{and } X(t_1^+) = X(t_2^+) = \dots = X(t_{N-1}^+) = u \quad 15(b)$$

This ensures that we have N sub-intervals i.e. no sub-interval is of "zero" duration

$$t_f = \int_{\frac{x_o v_o}{v_1}}^{ru} \frac{dx}{x \mu(x)} + \int_u^{ru} \frac{dx}{x \mu(x)} + \dots + \int_u^{x_f} \frac{dx}{x \mu(x)} \quad 15(c)$$

$$v_1 = r^{1-\frac{1}{N}} v_f \quad 15(d)$$

$$t_f = \int_{\frac{x_o v_o}{r^{1-\frac{1}{N}} v_f}}^{ru} \frac{dx}{x \mu(x)} + (N-2) \int_u^{ru} \frac{dx}{x \mu(x)} + \dots + \int_u^{x_f} \frac{dx}{x \mu(x)} \quad 15(e)$$

Here the variables to be found are u, r. So we have for optimal conditions

$$\frac{\partial x_f}{\partial u} = 0 \text{ and } \frac{\partial x_f}{\partial r} = 0$$

This yields

$$\mu(u) = \mu(ru) \quad 16(a)$$

$$\mu(ru) = \mu\left(\frac{x_o v_o}{r^{1-\frac{1}{N}} v_f}\right) \quad 16(b)$$

combining (16a-b), since we do not want the first-interval to be of zero duration

$$u = \left(\frac{x_o v_o}{r^{1-\frac{1}{N}} v_f}\right) \quad 16(c)$$

$$\left(s_F - \frac{u}{Y}\right) \left(s_F - \frac{ru}{Y}\right) = K_m K_i \quad 16(d)$$

The three equations 15(e), 16(c), 16(d) are solved simultaneously for a fixed v_f , t_f to obtain r, u, x_f under the optimal conditions.

(ii) Sequential Quadratic Programming (SQP):

The integral method proposed can not be applied when the initial conditions are non-stoichiometric. This case can be analysed using sequential quadratic programming. We discuss the solution methodology for two cases

- (i) When the duration is divided N equal sub-intervals.
- (ii) When the duration of each sub-interval is not constrained to be equal.

(i) Equal Intervals:

Here in fed-batch mode of operation, we divide the duration of the operation into n equal time intervals. The substrate feed is added at the beginning of each sub-interval. The volume of the reactor is constant in each interval. The optimisation problem is to determine the optimal feed pulses to maximise final cell mass concentration (X_f). We assume cell mass growth to be limited by one substrate as done earlier. Here the duration of each sub-interval is known ^{since} the total cycle time is fixed.

The differential equations which govern the system evolution are (1a-b). Constraints are imposed on the final reactor volume at the final time (t_f),

$$V(t_f) = V_f \quad (17)$$

The updating conditions at the beginning of each interval are the conditions (3a-b).

In this approach the different charges ΔV_i 's to be found for the optimal performance are chosen to satisfy the constraint. The numerical method used here is Sequential Quadratic Programming (SQP). The convergence of this method needs the accurate

determination of derivatives of the objective function with respect to manipulated variables, in this case pulses (ΔV_i).

The success of this method depends on the accurate computation of these derivatives. We have used state trajectory sensitivity method proposed by Rosen and Luus, 1991 to calculate the derivatives for faster convergence.

Calculation of sensitivity with respect to ΔV_i 's:

For the case of equal sub-intervals we recall that our objective function is X_f and that the manipulated variables are ΔV_i 's for $i = 1, \dots, N$

Differentiating 1a-b with respect to ΔV_j , we have for $j = 1, \dots, N$

$$\frac{\partial \dot{X}}{\partial \Delta V_j} = \frac{\partial \dot{X}}{\partial X} \frac{\partial X}{\partial \Delta V_j} + \frac{\partial \dot{X}}{\partial S} \frac{\partial S}{\partial \Delta V_j}$$

$$\frac{\partial \dot{S}}{\partial \Delta V_j} = \frac{\partial \dot{S}}{\partial X} \frac{\partial X}{\partial \Delta V_j} + \frac{\partial \dot{S}}{\partial S} \frac{\partial S}{\partial \Delta V_j}$$

$$\frac{d}{dt} \left(\frac{\partial X}{\partial \Delta V_j} \right) = \mu(S) \frac{\partial X}{\partial \Delta V_j} + \frac{X(\mu(S))^2}{\mu_m} \left[\frac{-K_m}{S^2} + \frac{1}{K_i} \right] \frac{\partial S}{\partial \Delta V_j} \quad 18(a)$$

similarly

$$\frac{d}{dt} \left(\frac{\partial S}{\partial \Delta V_j} \right) = \frac{-\mu(S)}{Y} \frac{\partial X}{\partial \Delta V_j} - \frac{X(\mu(S))^2}{Y\mu_m} \left[\frac{-K_m}{S^2} + \frac{1}{K_i} \right] \frac{\partial S}{\partial \Delta V_j}$$

$$j = 1, \dots, n, t_{j-1} < t < t_j \quad 18(b)$$

The four equations (1a-b, 18a-b) are to be solved simultaneously from t_{j-1}^+ to t_f where $j = 1, \dots, n$. The following updating conditions

for $j = 1, \dots, N$ are valid for the sensitivity functions

$$\frac{\partial X}{\partial \Delta V_j} (t_{j-1}^+) = -X(t_{j-1}^-) \frac{V_{j-1}}{V_j^2}$$

$$\frac{\partial S}{\partial \Delta V_j} (t_{j-1}^+) = + (S_F - S(t_{j-1}^-)) \frac{V_{j-1}}{V_j^2},$$

when $j > 1$ we should integrate only two equations 1(a-b) from t_0 to t_{j-1}^-

for $j = 1 \dots N-1$

$i = j+1, \dots, N$

$$\frac{\partial X}{\partial \Delta V_j} (t_{i-1}^+) = X(t_{i-1}^-) \frac{V_i - V_{i-1}}{V_i^2} + \frac{V_{i-1}}{V_i} \frac{\partial X}{\partial \Delta V_j} (t_{i-1}^-)$$

$$\frac{\partial S}{\partial \Delta V_j} (t_{i-1}^+) = \frac{(S(t_{i-1}^-) - S_F) (V_i - V_{i-1})}{V_i^2} + \frac{V_{i-1}}{V_i} \frac{\partial S}{\partial \Delta V_j} (t_{i-1}^-)$$

Integrating these equations from t_j^+ to t_N yields the $\frac{\partial X(t_f)}{\partial \Delta V_j}$

This will give the gradients of objective function with respect to manipulated variables, (the pulses).

(ii) Unequal Intervals:

In this approximation we divide the duration into N different intervals. Here we have $2N$ variables to be found for optimal performance. Our manipulated variables are the ΔV_i 's and Δt_i 's. For this case we have to find the derivatives with respect to ΔV_i 's as well as Δt_i 's. The calculation of gradients with respect to ΔV_i 's are the same as discussed above. The calculation of gradients with respect to Δt_i 's as follows.

Differentiating 1a-b with respect to ΔV_j , we have

$$\frac{\partial \dot{X}}{\partial \Delta t_j} = \frac{\partial \dot{X}}{\partial X} \frac{\partial X}{\partial \Delta t_j} + \frac{\partial \dot{X}}{\partial S} \frac{\partial S}{\partial \Delta t_j}$$

$$\frac{\partial \dot{S}}{\partial \Delta t_j} = \frac{\partial \dot{S}}{\partial X} \frac{\partial X}{\partial \Delta t_j} + \frac{\partial \dot{S}}{\partial S} \frac{\partial S}{\partial \Delta t_j}$$

$$\frac{\partial \dot{X}}{\partial \Delta t_j} = \mu(S) \frac{\partial X}{\partial \Delta t_j} + \frac{X(\mu(S))^2}{\mu_m} \left[\frac{-K_m}{S^2} + \frac{1}{K_i} \right] \frac{\partial S}{\partial \Delta t_j} \quad 20(a)$$

similarly

$$\frac{d}{dt} \left(\frac{\partial S}{\partial \Delta t_j} \right) = \frac{-\mu(S)}{Y} \frac{\partial X}{\partial \Delta t_j} + \frac{X(\mu(S))^2}{Y\mu_m} \left[\frac{-K_m}{S^2} + \frac{1}{K_i} \right] \frac{\partial S}{\partial \Delta t_j}$$

$$j = 1, \dots, n, t_{j-1} < t < t_j \quad 20(b)$$

The four equations 1(a-b), 20(a-b), are to be simultaneously integrated from t_0^+ to t_f . We can do it otherwise eliminating unnecessary computations.

Suppose if we differentiate with respect to j^{th} time interval then integrate the equations from t_j^+ to t_f . Because

$$\left. \frac{\partial X}{\partial \Delta t_j} \right|_{t=t_j^-} = \left. \frac{dX}{dt} \right|_{t=t_j^-}$$

$$\left. \frac{\partial S}{\partial \Delta t_j} \right|_{t=t_j^-} = \left. \frac{dS}{dt} \right|_{t=t_j^-}$$

The updating conditions are

$$\frac{\partial X}{\partial \Delta t_j} (t_{j-1}^+) = \frac{V_{j-1}}{V_j} \frac{\partial X}{\partial \Delta t_j} (t_{j-1}^-)$$

$$\frac{\partial S}{\partial \Delta t_j} (t_{j-1}^+) = \frac{V_{j-1}}{V_j} \frac{\partial S}{\partial \Delta t_j} (t_{j-1}^-)$$

The effect of initial conditions on the optimal feed profile and the objective function is also tabulated.

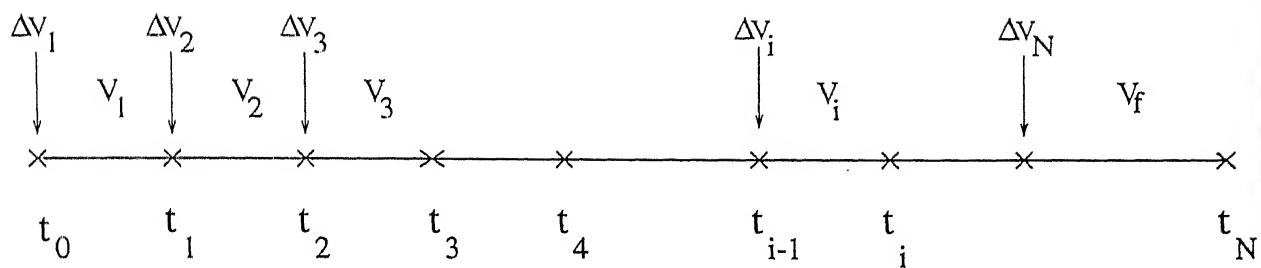


Fig. 1. The variables in the different stages of a cycle.

CHAPTER 3

Result and Discussions

In this section we discuss the results of the computations obtained using the methods discussed earlier. We divide this section into two parts. Part 1, consists of results obtained using the integral method, non-stoichiometric equal and unequal intervals for the case of fixed t_f and fixed V_f . Part 2 deals with the results obtained for remaining three modes of reactor operations.

In our approach we have described the entire period of operation into 'N' sub-intervals. The volume of the reactor is increased from V_0 to V_f by adding pulses ΔV_i at the beginning of the i^{th} sub-interval. For the case of equal time intervals the problem reduces to determining the N-variables, ΔV_i 's to maximise X_f .

For the case of unequal sub-intervals, we have to obtain 2N variables, the pulses to be added at the beginning of the sub-intervals, as well as their durations.

PART 1:

The integral method can be used only when the biomass 'X' and the substrate concentration 'S' satisfy the stoichiometric relationship. This enables us to reduce the two dimensional system to a one-dimensional system. The optimal profile of the pulses is obtained by the simultaneous solution of the three equations 15(e), 16(c), 16(d) for u , r and X_f . The parameters chosen for simulation are $K_m = 0.397458$, $K_i = 62.9$,

$\mu_m = 0.347695$, $Y = 0.2$, $S_F = 10$, $X_O = 1.0$, $V_O = 1.0$, $V_f = 2.5$,
 $T_f = 5$.

In Table-1 we depict the numerical results of the computations for different values of 'N', the number of sub-intervals. The first (N-1) sub-intervals are of equal duration while the last sub-interval is distinct from these. We have also depicted the corresponding u - the biomass concentration, r - the ratio of the reactor volumes of successive intervals i.e., V_{i+1}/V_i , ($i = 1, \dots, n-1$), and X_f the biomass at the end of the duration.

The biomass concentration X_f increases with the number of pulses. This confirms our expectations as increasing N results in obtaining a better approximation. In the batch mode the biomass concentration is 1.7537.

The improvement in the performance when operated in the fed-batch mode in this case is marginal. For the choice of parameters listed here the fed-batch reactor gives only a 0.542% improvement over the batch reactor for $N=10$. Fig. 2a depicts the variation of reactor volume for $N=5$. The corresponding variation of X is shown in Fig. 2b. The addition of the pulses results in discontinuities in the biomass concentrations.

The integral method proposed here has some inherent limitations. The method can converge to infeasible solutions. Thus although $r > 1$, $u > 0$ and $X_f > 0$, $V_1 = V_f r^{1-n}$, may be less than V_O . This solution is not feasible since it yields $V_1 < V_O$. Such solutions do satisfy the equations but however are physically meaningless.

A tacit assumption in the integral method is that we add pulses at the beginning of each sub-interval. Clearly a solution to the equations is that some of the pulses are zero, i.e., $r = 1$, for some cases, while for others $r > 1$. We have not considered this case. This method also implies that the duration of a sub-interval is zero when $r = 1$. It does not consider the possibility of reactor operation when the i^{th} pulse can be zero, and the duration of the i^{th} sub-interval is non-zero.

The optimum value reported as in Table-1 is hence subject to these tacit assumptions.

Sequential Quadratic Programming:

For the case when the initial conditions do not satisfy the stoichiometric relationship we can not use the integral method discussed above since now the problem is two dimensional. We have solved this problem using Sequential Quadratic Programming. The function 'CONSTR' available in MATLAB ^{was} used to solve this problem.

Equal Sub-intervals:

In this method all sub-intervals are considered to be of equal durations. We consider the operation where the final reactor volume and the duration of the entire cycle are both externally fixed. The duration of each sub-interval is hence determined once we fix 'N'. Hence in this problem one has to determine only the N-pulses, i.e., ΔV_i 's which maximises $X(t_f)$.

In this mode of reactor operation the optimal profile will be dependent on the initial state of the reactor. There are three characteristic quantities which characterize the substrate

concentration, S_0 , the initial substrate concentration, S_F the feed concentration, S^* the concentration where $\mu(S)$ has a maximum.

The relative ordering of the different quantities gives rise to different cases. These have been tabulated in Table 2. The performance of the reactor i.e., the sequence of the pulses for each of these cases is tabulated in Table 3 for fixed $V_f = 10$, $t_f = 30$ and $N=5$.

We now discuss the trends of the optimal profile obtained in Table 3, for the different conditions.

Case I: $S_0 < S^* < S_F$: The initial concentration is lower than the S^* . Since the reaction rate is maximum at S^* , the performance is optimal when the substrate concentration is maintained closer to S^* . It is hence necessary to add the first pulse to increase S_0 to S^* . The optimal pulse distribution which satisfies all constraints is shown in Table 3. The optimal X_f here is 2.8372. For this case the batch operation has an $X_f = 1.6012$. Fig. 3a depicts the volume of the reactor after the addition of each pulse. The volume changes discontinuously at the point of addition of each pulse. The corresponding biomass and substrate concentrations are shown in Fig. 3b(i) and Fig. 3b(ii).

Case II: $S_F < S^* < S_0$: In case 2a, S_0 is approximately S^* and S_F is very low. Addition of S_F will hence hurt the reactor performance. The pulse addition is hence delayed till the end. This addition is necessary since we have to satisfy the volume constraint. For case 2b, S_0 is significantly higher than S^* . Addition of S_F reduces S_0 to S^* now and this yields the optimal profile shown. Here the fed-batch performance is same as batch.

Case III: $S_O < S_F < S^*$: Since the initial concentration is low addition of the feed increases the substrate concentration close to S^* . Here it is advantageous to add all the pulses in the first sub-intervals as this brings S_O closest to S^* . In this case the final biomass concentration is same for fed-batch and batch reactors.

Case IV: $S^* < S_F < S_O$: Here the first pulse is added as in case III, at the first sub-interval. This brings S_O closest to S^* and the reaction rate is closest to the maximum. Here again the performance of the fed-batch and batch reactors are identical.

Case V: $S^* < S_O < S_F$: Here the initial concentration is closer to S^* than S_F . Addition of the feed would thus increase S_O and lower the reaction rate. This addition should be hence delayed as far as possible. This confirms the trend shown in the table.

Case VI: $S_F < S_O < S^*$: Here again addition of the feed would drive the concentration away from S^* , lowering the reaction rate. Hence this should be delayed. In this case the substrate is added in the last interval to satisfy the volume constraint.

Unequal Sub-intervals (Fixed t_f and Fixed V_f):

In Table-4 we depict the results of the computations for the case of unequal time intervals. Here $t_f = 30$, and $V_f = 10$. We have presented the results for the same N as in Table-3. This enable us to compare the two results.

The qualitative trends of the two Tables agree well. The performance of each case for a given 'N' is better when the intervals are of unequal duration as compared to when we

restrained the intervals to be equal.

We simulated the behaviour of the system for the case of stoichiometric initial conditions with SQP algorithm for unequal sub-intervals. The parameters set chosen is the one used to generate the results using the integral method. The SQP method also yields the same optimal profile as the integral method. The length of $(N-1)$ sub-intervals is equal and the last one is distinct. The successive volumes V_{i+1}/V_i also bear a constant ratio for $i=1,2,\dots,N$. The optimal objective function also matches to within a desired numerical accuracy with the results in (Table-1).

PART 2:

We now discuss the application of this method to remaining three modes of reactor operation (i) fixed final time, free final volume (ii) free final time and fixed final volume (iii) free final time, and free final volume.

The optimisation problem solved so far have some cases where the volume of the reactor is made up in the last sub-interval. This is forced on the system since it has to satisfy the constraint on the reaction volume. It would hence appear that should this constraint be removed the optimal profile be one in which no pulses are added. To test this hypothesis removed the constraint on the reaction volume. We now discuss the results for the situation when the reactor is operated over a time t_f and the final free volume V_f .

For cases 2, 4, 6 of Table-5, here, there is no pulse added for optimal performance. The optimal performance is in batch mode with reactor volume equal to the initial volume. hence the final pulse added for the fixed volume problems, in Table-4 is only to satisfy the constraint of the fixed final volume.

For cases 1, 5 pulses are added in each sub-intervals. The final volume for both the cases is less than 10. In case 1: $V_f = 7.96$, while for case 5 it is 7.1925. The corresponding cases in Table-4, also have non-zero pulses being added in each sub-interval.

For case 3, the optimal performance is found when the initial pulse is non-zero as in Table-3. For this case the optimisation is carried out by constraining the final volume V_f to be lower than the upper bound. The upper bound chosen for this case study was

20. The reactor is filled in the first pulse, since this raises S_0 closer to S^* . This is again identical to the optimal profile in Table-4.

One would expect a similar trend for case 4, i.e., addition in the first pulse to being S_0 to S^* . However, for the values chosen S_0 , S_F are very closer to S^* and hence batch mode at V_0 is optimal.

The improvement of the performance as measured by the concentrations X_f for each case in Table-5 is much better than for the corresponding cases in Table-4. The free volume problem has a better performance than the reactor with a fixed final volume.

The optimal performance for a given number of pulses may not be necessarily obtained when the sub-intervals are of the same duration. The constraint of each sub-intervals results in obtaining a sub-optimal profile for a given N .

To obtain a time optimal profile for a fixed number of intervals N , we now discuss the results obtained when the sub-intervals are of unequal durations. Now for a given number of N sub-intervals we have to determine $2N$ variables, the $N \Delta t_i$'s and the $N \Delta V_i$'s. We solve this problem also using "CONSTR" of MATLAB. The convergence of the algorithm is based on the accurate calculation of the sensitivities of the objective function with respect to the control variables. These are computed as discussed earlier.

In Table-6, we depict the results for fixed t_f and free V_f , with unequal sub-intervals. The effect of initial conditions on the optimal profile is similar to that predicted in Table-5. For each case the optimal solution is better when we relax the

constraints of equal sub-intervals as expected.

Table-7, contains the results for $V_f = 10$, and free t_f . The solution method requires an upper bound on free time. This was fixed at 150. In most of the cases as shown the optimal profile was found such that the cycle time was 150. A characteristic feature of most of the runs in that the system posses multiple optima.

The convergence to the different optima depends on the initial guesses supplied. Although the profile can be very different there is no change in the objective function. For this mode the improvement in the objective function over the batch mode is negligible in most cases. This occurs because the system tends to choose the largest possible time to allow the reaction to go to completion. This results in maximum biomass.

Table-8 depicts the results for the free V_f and free t_f problem. Here again we have to impose upper bounds on these variables to the optimal profile obtained in most cases is when the reactor is operated in the batch mode. The choice of t_f , V_f here is such that the biomass X_f at the end of the cycle is much more than that obtained in the earlier modes of operation for each combination of S_0 , S^* , S_F . The corresponding biomass and substrate concentrations for unequal intervals are shown in Fig.4b(i) and Fig.4b(ii).

Table-9 contains the results for $V_f = 10$, and free t_f for equal intervals of time. We impose an upperbound on free time. This was fixed at 2500. The convergence to the different optima depends on the initial guesses supplied. Here also the performance of fed-batch reactor is almost equal to the batch

mode.

Table-10 depicts the results for free V_f and free t_f problem. Here we impose an upper bound on these variables. The optimal profile obtained in most cases is when the reactor is operated in the batch mode.

CHAPTER 4

Conclusions

Here we have demonstrated different methods which can be used to obtain the optimal performance of fed-batch reactions. The flow rate over the entire cycle is approximated by discretised pulses.

The integral method is applicable only when the initial conditions are stoichiometric. It is also tacitly assumes that all pulses are non-zero.

Sequential quadratic programming allows us to obtain optimal profiles for the case of non-stoichiometric initial conditions. The effect of S_0 , S_F , S^* has been studied and explained qualitatively.

The numerical convergence of SQP algorithm requires the accurate computation of the sensitivities. An efficient way to evaluate these is discussed.

For a particular set of parameters the case of stoichiometric unequal intervals yields the best possible optimal solution. The SQP method for the stoichiometric case can yield optimal profile even when the integral method gives infeasible solution.

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Table 1

Integral Method

N	$(N-1)\Delta t$'s	Δt_n	u	r	X_f
batch (N=1)	0	5.0	-	-	1.7537
3	1.1818	2.6363	0.8125	1.4252	1.7623
5	0.6714	2.3142	0.8952	1.2231	1.763
7	0.4675	2.1954	0.9277	1.1505	1.7632
10	0.3207	2.1136	0.9508	1.1010	1.7632

Table 2

Parameters used for Table (3-10) are $\mu_m = 0.208$, $K_m = 2.516$,
 $K_i = 25$, $Y = 0.8$, $X_o = 0.1$, $v_o = 7$, $S^* = 7.93095$

Case	S_o	S_F	Description
1	0.142857×10^{-3}	75	$S_o < S^* < S_F$
2a	8	0.142857×10^{-3}	$S_F < S^* < S_o$
2b	20	4	$S_F < S^* < S_o$
3	0.142857×10^{-3}	5.0	$S_o < S_F < S^*$
4a	8	7.95	$S^* < S_F < S_o$
4b	20	10	$S^* < S_F < S_o$
5a	7.95	75	$S^* < S_o < S_F$
5b	10	75	$S^* < S_o < S_F$
6	3.0	1.0	$S_F < S_o < S^*$

Table 3

Non-stoichiometric, Equal Intervals of Time, Fixed T_f , Fixed V_f

Case	ΔV_1	ΔV_2	ΔV_3	ΔV_4	ΔV_5	Fed-batch X_f	Batch X_f
1	0.8343	0.0226	0.0487	0.1057	1.9888	2.8372	1.6012
2a	-	-	-	-	3.0	2.7845	2.5542
2b	3.0	-	-	-	-	2.4624	2.4624
3	3.0	-	-	-	-	0.5493	0.5493
4a	1.5294	1.4706	-	-	-	3.0911	3.0911
4b	3.0	-	-	-	-	2.212	2.212
5a	0.0047	0.00224	0.0486	0.1064	2.818	2.6703	1.1918
5b	-	-	-	-	3.0	2.5857	1.11945
6	-	-	-	-	3.0	1.157	1.001

Table 4

Non-stoichiometric, Unequal Intervals Fixed T_f and Fixed V_f

Case		i					Fed-batch X_f	Batch X_f
		1	2	3	4	5		
1	ΔV_i	0.8577	0.1122	0.1518	0.1847	1.6926	3.1817	1.6012
	Δt_i	15.805	6.692	4.31	3.20	-		
2a	ΔV_i	-	-	-	-	3	2.967	2.5542
	Δt_i	8.1178	8.1195	8.1195	5.6432	-		
2b	ΔV_i	3.0	-	-	-	-	2.4624	2.4624
	Δt_i	5.578	5.9645	6.095	6.158	6.204		
3	ΔV_i	3.0	-	-	-	-	0.5493	0.5493
	Δt_i	5.849	5.9744	5.975	6.036	6.170		
4a	ΔV_i	0.762	0.761	0.76	0.717	-	3.0911	3.0911
	Δt_i	1.968	3.968	5.968	7.979	10.117		
4b	ΔV_i	3.0	-	-	-	-	2.2120	2.2120
	Δt_i	7.64	7.78	7.78	6.81	-		
5a	ΔV_i	0.028	0.1131	0.1518	0.1851	2.522		
	Δt_i	15.7815	6.697	4.315	3.21	-	3.1808	1.198
5b	ΔV_i	-	-	-	0.2271	2.7729	3.1248	1.1195
	Δt_i	9.354	8.804	7.447	4.3956			
6	ΔV_i	-	-	-	-	3.0		
	Δt_i	9.881	9.9806	10.081	0.0587	-	1.17895	1.0096

Table 5

Non-stoichiometric, Equal Intervals of Time, Fixed T_f , Free V_f

Case	ΔV_1	ΔV_2	ΔV_3	ΔV_4	ΔV_5	Fed-batch X_f	Batch X_f
1	0.8343	0.0226	0.0487	0.0953	0	3.92424	3.8938
2a	-	-	-	-	-	4.23861	4.23861
2b	-	-	-	-	-	2.6805	2.6805
3	10.094	-	-	-	-	0.8469	0.8469
4a	-	-	-	-	-	4.23861	4.23861
4b	-	-	-	-	-	2.6805	2.6805
5a	0.0046	0.0226	0.0487	0.1060	0.0106	4.36098	4.3077
5b	-	-	-	-	-	4.4159	4.4159
6	-	-	-	-	-	4.23861	4.23861

Table 6

Non-stoichiometric, Unequal Intervals Fixed T_f and Free V_f

Case		i					Fed-batch X_f	Batch X_f
		1	2	3	4	5		
1	ΔV_i	0.8419	0.0432	0.0547	0.0644	-	3.9245	3.8924
	Δt_i	10.312	5.4711	3.7455	5.3416	5.1308		
2a	ΔV_i	-	-	-	-	-		
	Δt_i	5.806	5.9048	6.0029	6.0976	6.1876	4.2386	4.2386
2b	ΔV_i	-	-	-	-	-		
	Δt_i	5.9989	5.9990	6.001	6.001	6.002	2.6805	2.6805
3	ΔV_i	10.094	-	-	-	-	0.84696	0.84696
	Δt_i	2.5047	6.0501	6.8642	7.2006	7.3804		
4a	ΔV_i	-	-	-	-	-	4.2386	4.2386
	Δt_i	5.801	5.901	6.001	6.101	6.1964		
4b	ΔV_i	-	-	-	-	-		
	Δt_i	5.4717	5.8039	6.1004	6.2575	6.366	2.6805	2.6805
5a	ΔV_i	0.0134	0.0482	0.0614	0.0727	-	4.36719	4.3057
	Δt_i	10.8834	5.6831	3.8212	3.7499	5.8624		
5b	ΔV_i	-	-	-	-	-		
	Δt_i	7.673	7.673	6.226	4.9555	4.067	4.4159	4.4159
6	ΔV_i	-	-	-	-	-		
	Δt_i	6.003	6.003	6.003	6.003	5.988	1.68421	1.68421

Table - 7

Unequal Intervals of Time, Fixed Final Volume, and Free Final Time

Case		i					Fed-batch	Batch
		1	2	3	4	5	X_f	X_f
1	ΔV_i	0.2601	2.7399	-	-	-	18.07	18.07
	Δt_i	10.119	9.503	21.064	9.7196	10.689		
2a	ΔV_i	-	-	-	0.8429	2.1571	4.55	4.55
	Δt_i	30.016	30.116	30.216	30.189	29.462		
2b	ΔV_i	1.4175	0.6373	-	-	0.9452	12.23	12.23
	Δt_i	28.827	29.09	29.34	30.26	32.49		
3	ΔV_i	3.0	-	-	-	-	1.2708	1.2708
	Δt_i	-	2.0399	3.91	52.72	91.34		
4a	ΔV_i	1.5854	0.8037	0.204	0.204	0.204	6.458	6.458
	Δt_i	29.8	29.9	30.0	30.1	30.2		
4b	ΔV_i	1.1024	0.2938	-	0.2059	1.3979	13.67	13.67
	Δt_i	29.511	29.356	29.554	30.2	31.73		
5a	ΔV_i	0.7125	2.2875	-	-	-	22.522	22.522
	Δt_i	29.8195	23.05	3.953	-	1.264		
5b	ΔV_i	3.0	-	-	-	-	23.67	23.67
	Δt_i	80.88	41.36	1.27	-	11.83		
6	ΔV_i	1.6178	1.3822	-	-	-	1.99	1.99
	Δt_i	45.813	38.49	31.15	23.29	11.254		

Table - 8
Unequal Intervals of Time, Free Final Volume, and Free Final Time

Case		i					Fed-batch X_f	Batch X_f
		1	2	3	4	5		
1	ΔV_i	0.0154	1.8217	0.0113	1.2379	89.8138	55.807	11.76
	Δt_i	2.5	48.361	5.281	6.953	70.744		
2a	ΔV_i	-	-	-	-	-	6.5	6.5
	Δt_i	16.37	16.47	16.57	16.67	16.77		
2b	ΔV_i	-	-	-	-	-	16.1	16.1
	Δt_i	14.12	14.22	14.32	14.42	14.52		
3	ΔV_i	146.685	0.6511	4.6065	14.098	26.8596	3.8635	3.8635
	Δt_i	161.36	162.77	163.77	164.77	166.1		
4a	ΔV_i	-	-	-	-	-	8.1	8.1
	Δt_i	13.461	13.56	13.66	13.77	13.86		
4b	ΔV_i	-	-	-	-	-	16.1	16.1
	Δt_i	15.45	16.45	17.45	18.45	19.43		
5a	ΔV_i	0.6945	3.884	0.1977	0.7982	87.4255	56.2522	22.36
	Δt_i	29.0819	42.09	20.74	10.693	41.407		
5b	ΔV_i	0.694	3.88	0.197	0.798	87.43	56.37	21.96
	Δt_i	29.1	42.1	20.7	10.69	41.0		
6	ΔV_i	-	-	-	-	-	2.5	2.5
	Δt_i	45.0	38.0	31.0	23.0	11.0		

Table - 9

Equal Intervals of Time, Fixed Final Volume, and Free Final Time

Case	Δt	ΔV_1	ΔV_2	ΔV_3	ΔV_4	ΔV_5	Fed-batch X_f	Batch X_f
1	56.45	3.0	-	-	-	-	18.0701	18.0701
2a	45.954	-	-	-	0.52	2.48	4.55	4.55
2b	17.098	1.8931	0.9501	0.1567	-	-	12.23	12.23
3	169.927	3.0	-	-	-	-	1.2701	1.2701
4a	192.236	0.0001	0.0004	0.0003	0.0003	2.9988	6.458	6.458
4b	14.684	-	0.4368	-	-	2.5632	13.67	13.67
5a	67.811	-	1.7762	1.2238	-	-	22.52	22.52
5b	55.474	3.0	-	-	-	-	23.67	23.67
6	44.691	0.186	1.8868	0.927	-	-	1.99	1.99

Table - 10

Equal Intervals of Time, Free Final Volume, and Free Final Time

Case	Δt	ΔV_1	ΔV_2	ΔV_3	ΔV_4	ΔV_5	Fed-batch X_f	Batch X_f
1	30.0	4.82	-	5.41	9.4	73.4	55.81	52.27
2a	16.76	-	-	-	-	-	6.5	6.5
2b	29.1	-	-	-	-	-	16.1	16.1
3	29.97	93.0	-	-	-	-	3.727	3.7065
4a	16.06	-	-	-	-	-	6.5	6.5
4b	15.89	-	-	-	-	-	16.1	16.1
5a	29.77	42.022	0.004	0.005	1.536	49.43	56.252	33.416
5b	29.948	0.0663	2.1801	-	8.9635	81.7902	56.367	35.561
6	24.24	-	-	-	-	-	2.5	2.5

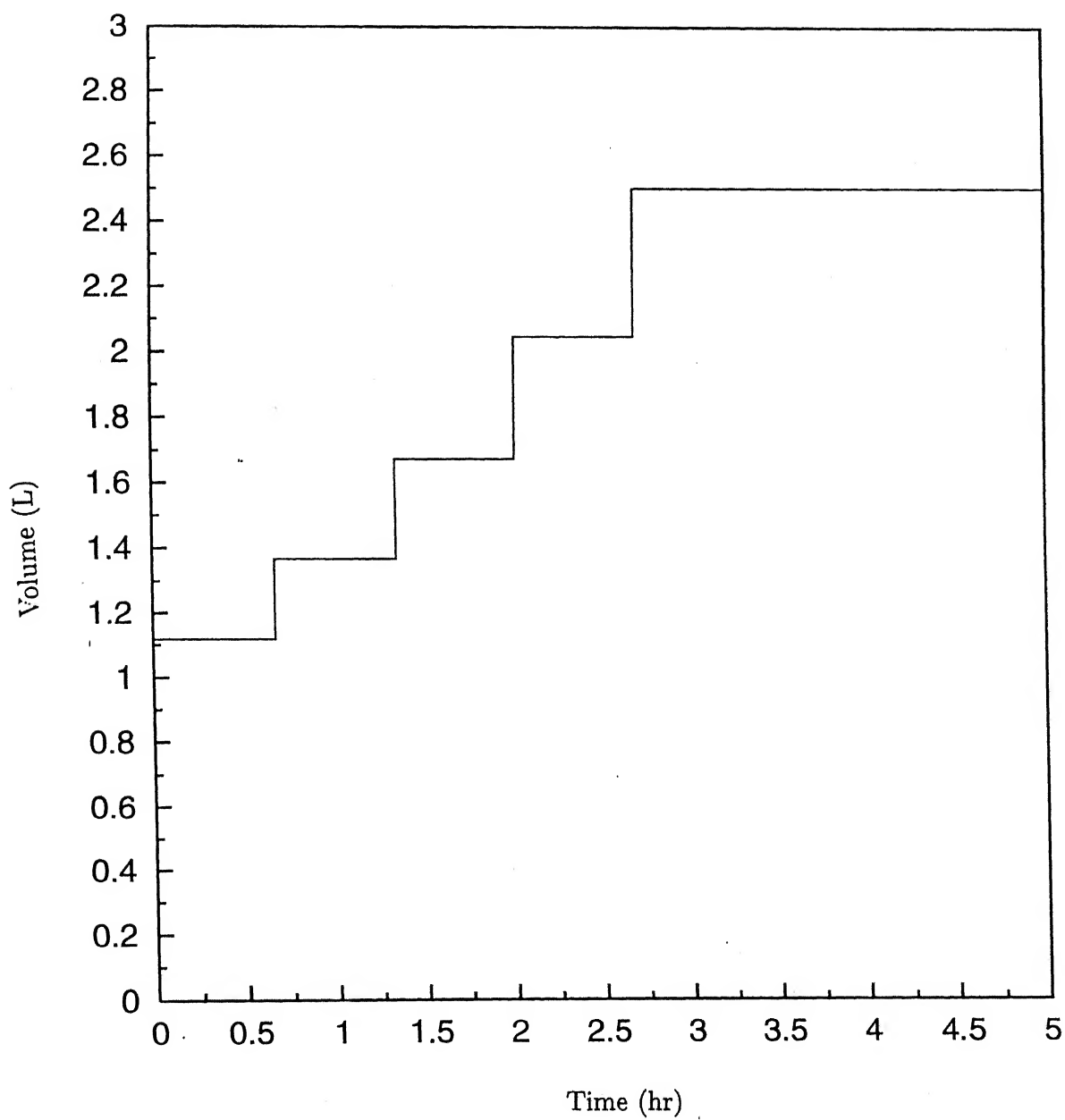


Fig. 2a : Volume profile for integral method $N=5$.

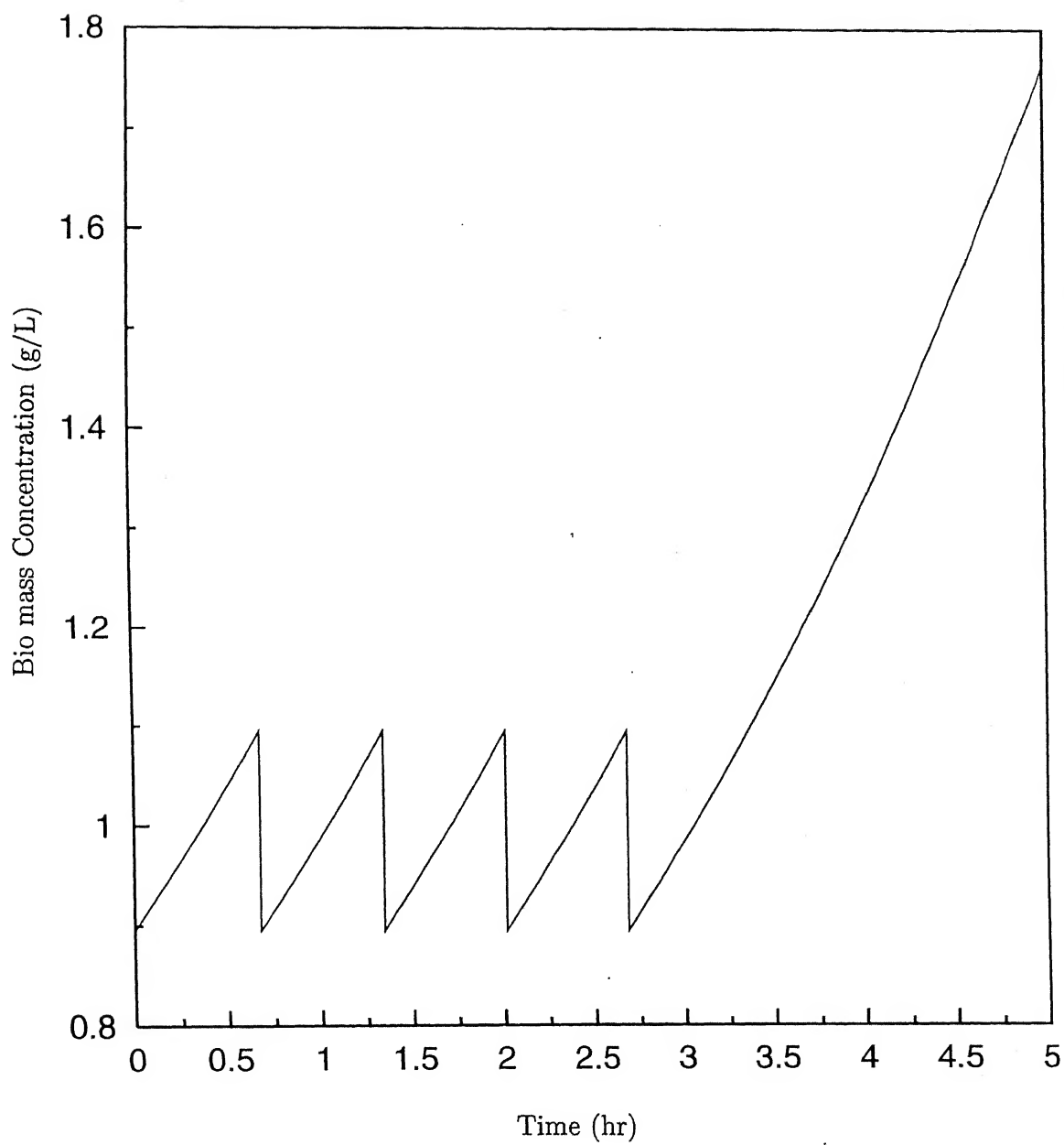


Fig. 2b : Biomass concentration profile for integral
N=5

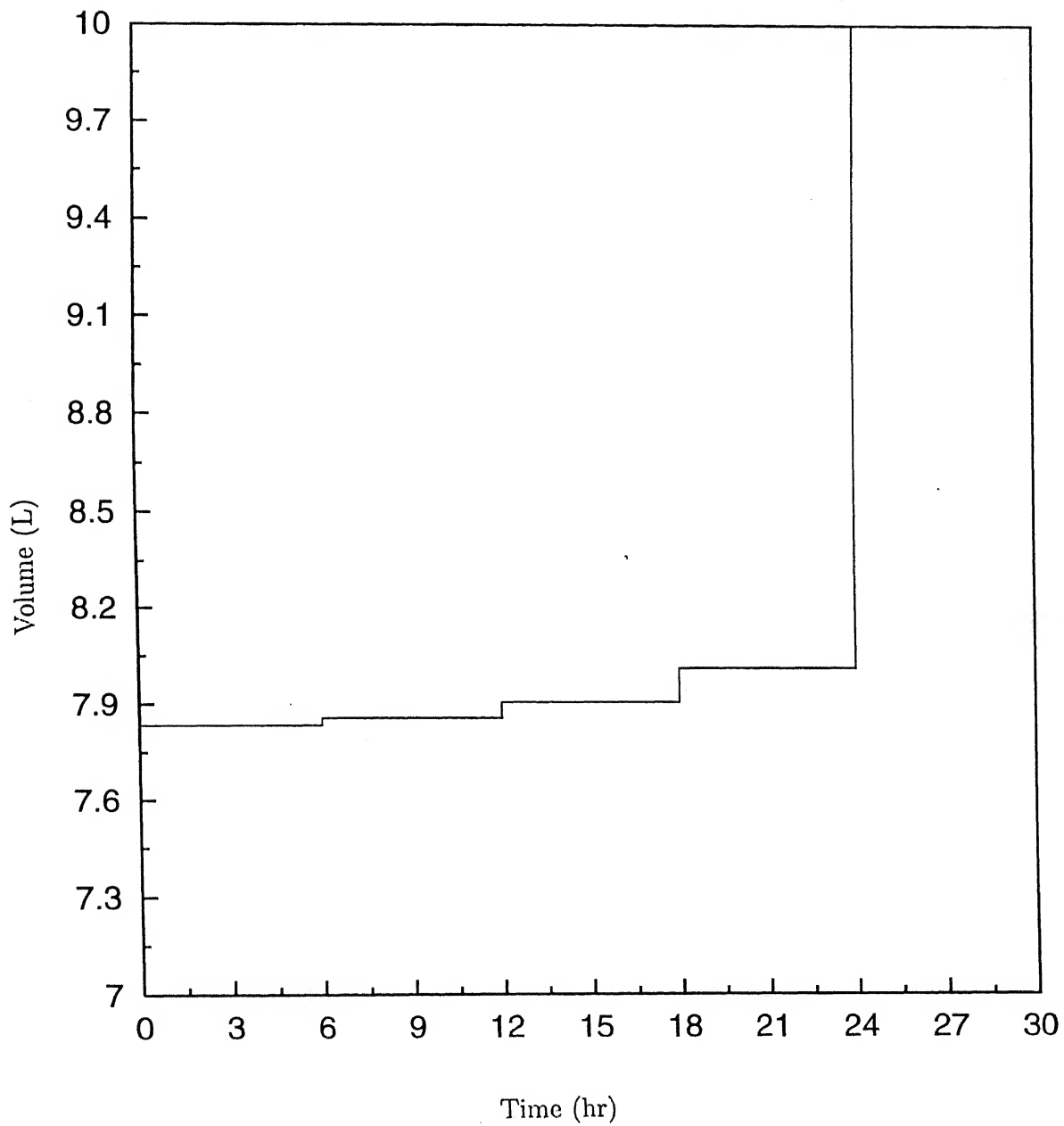


Fig. 3a : Volume profile for the fixed V_f and t_f with equal intervals.

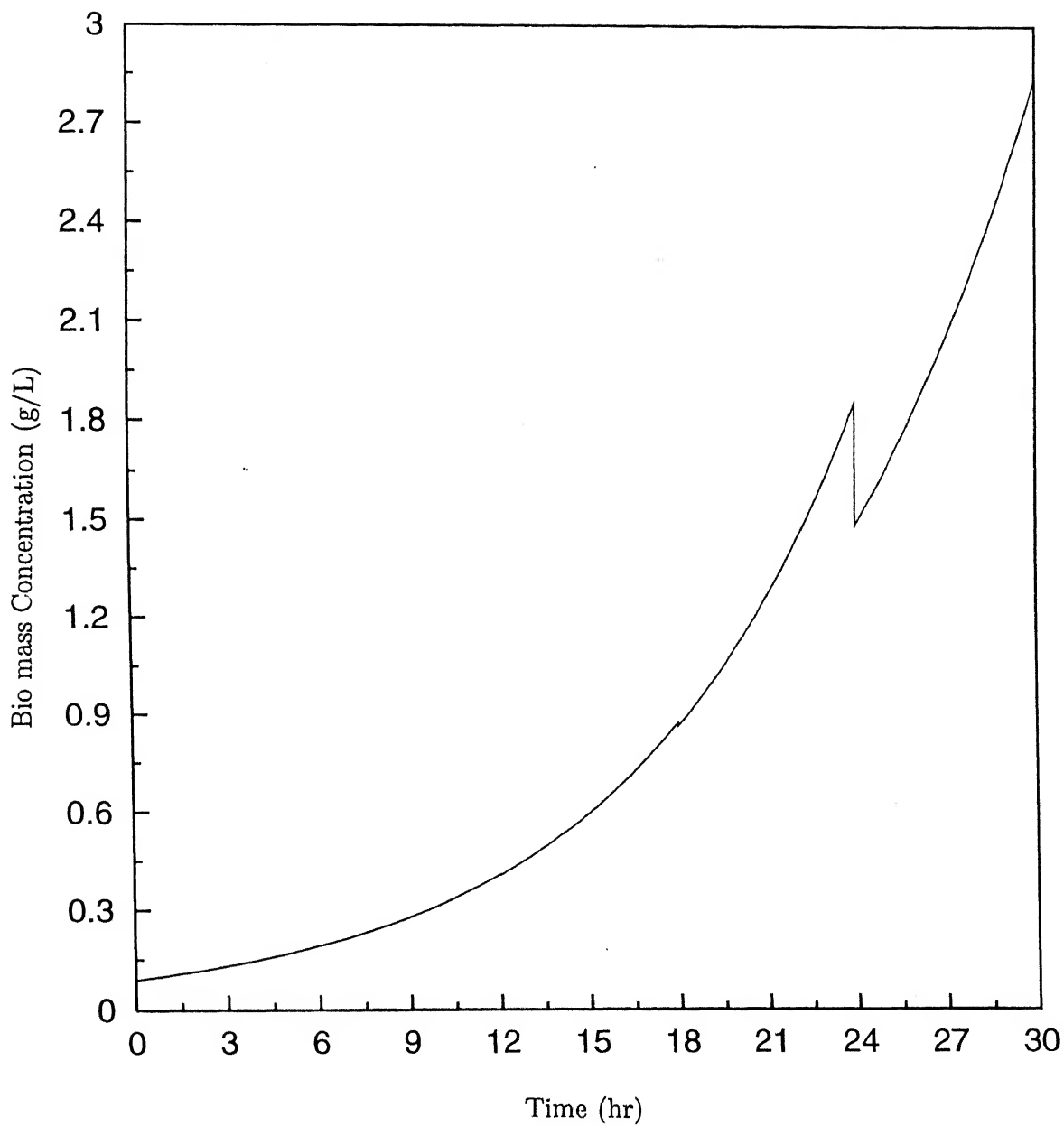


Fig. 3b(i) : Biomass concentration profile for the fixed V_f and t_f with equal intervals.

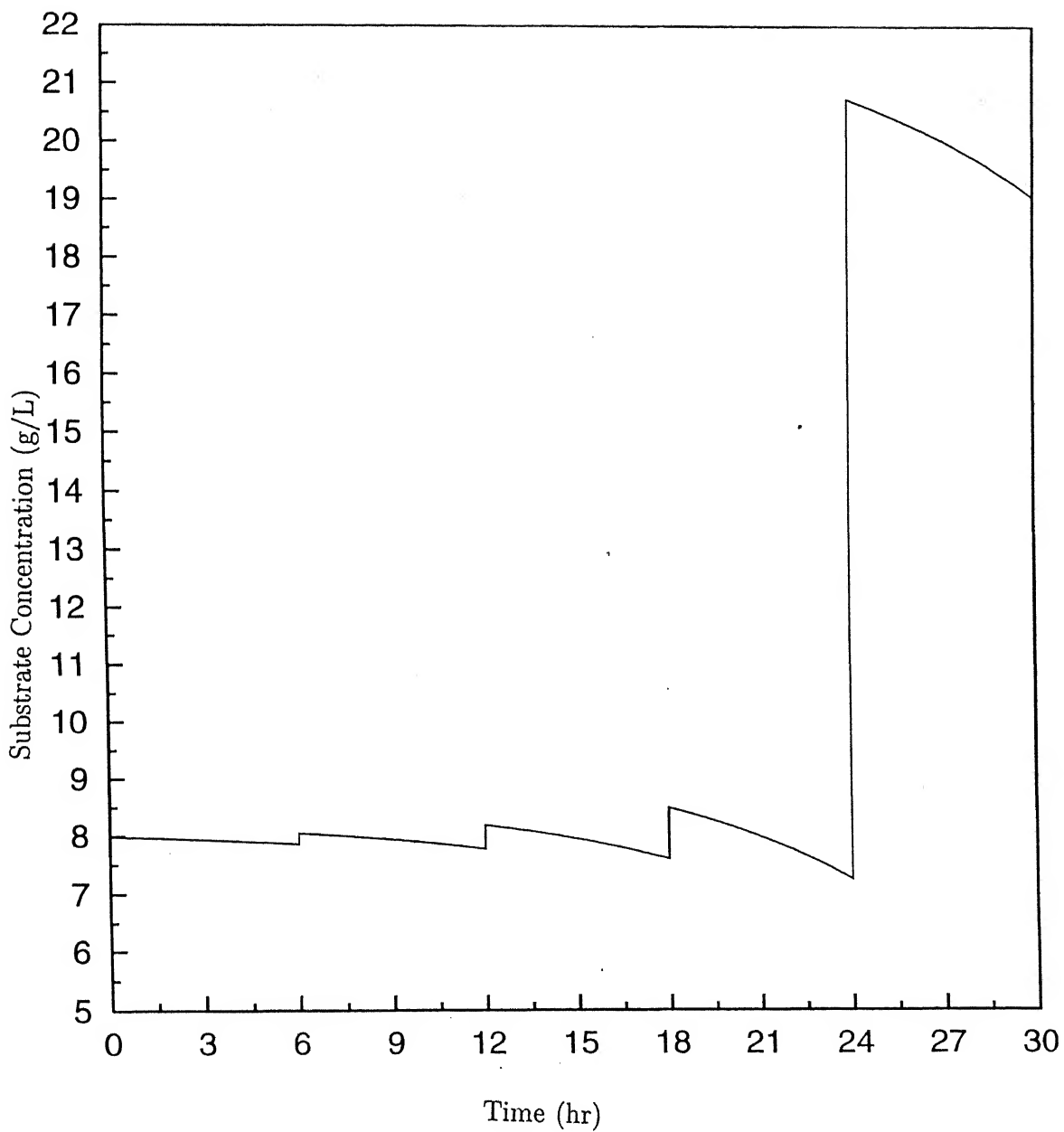


Fig. 3b(ii) : Substrate concentration profile for the fixed V_f with equal intervals.

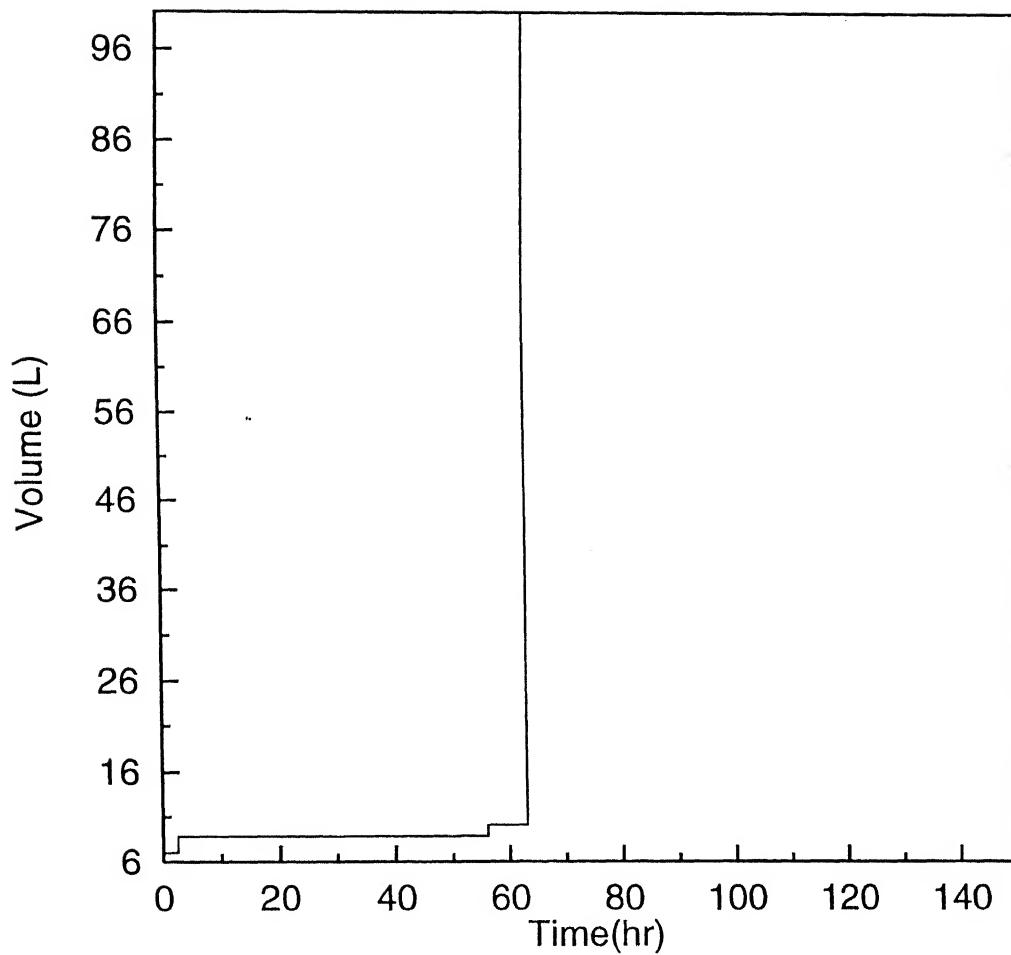


Fig. 4a : Volume profile for the Free V_f and t_f with unequal intervals.

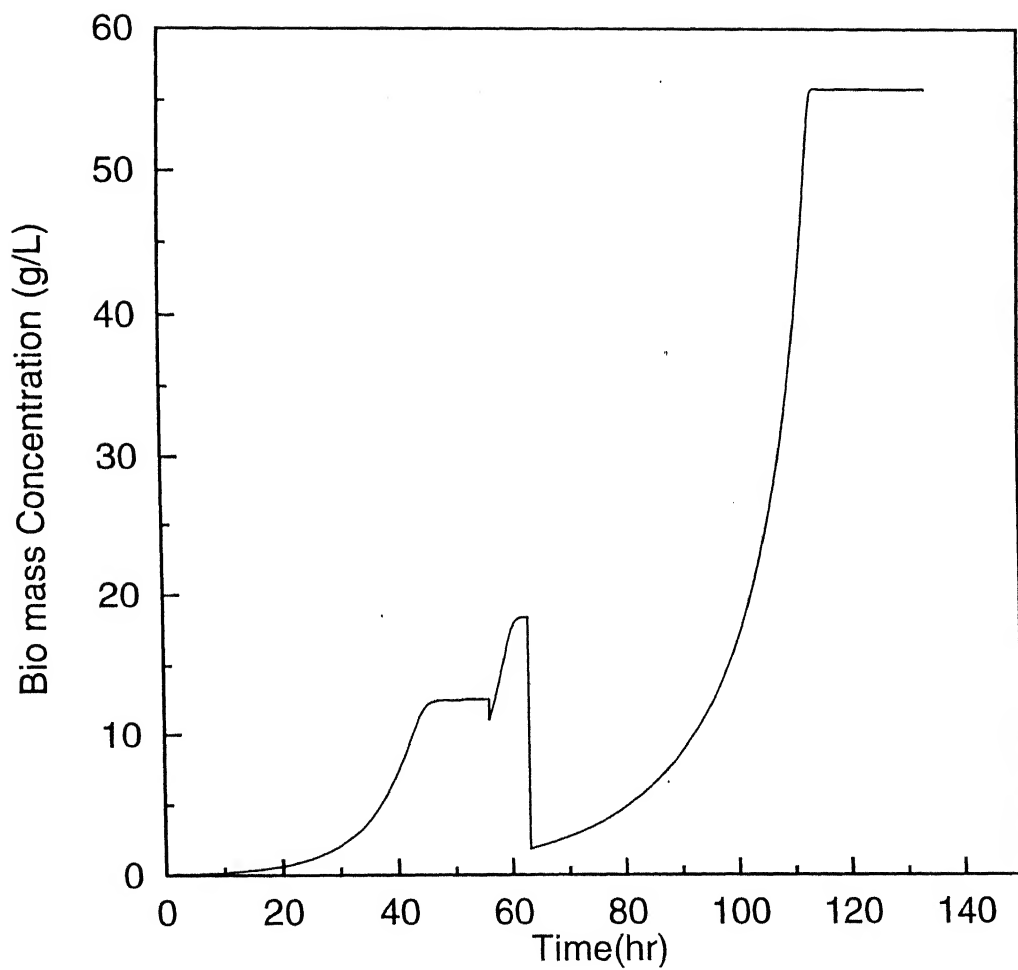


Fig. 4b(i) : Biomass concentration profile for the free V_f and t_f with unequal intervals.

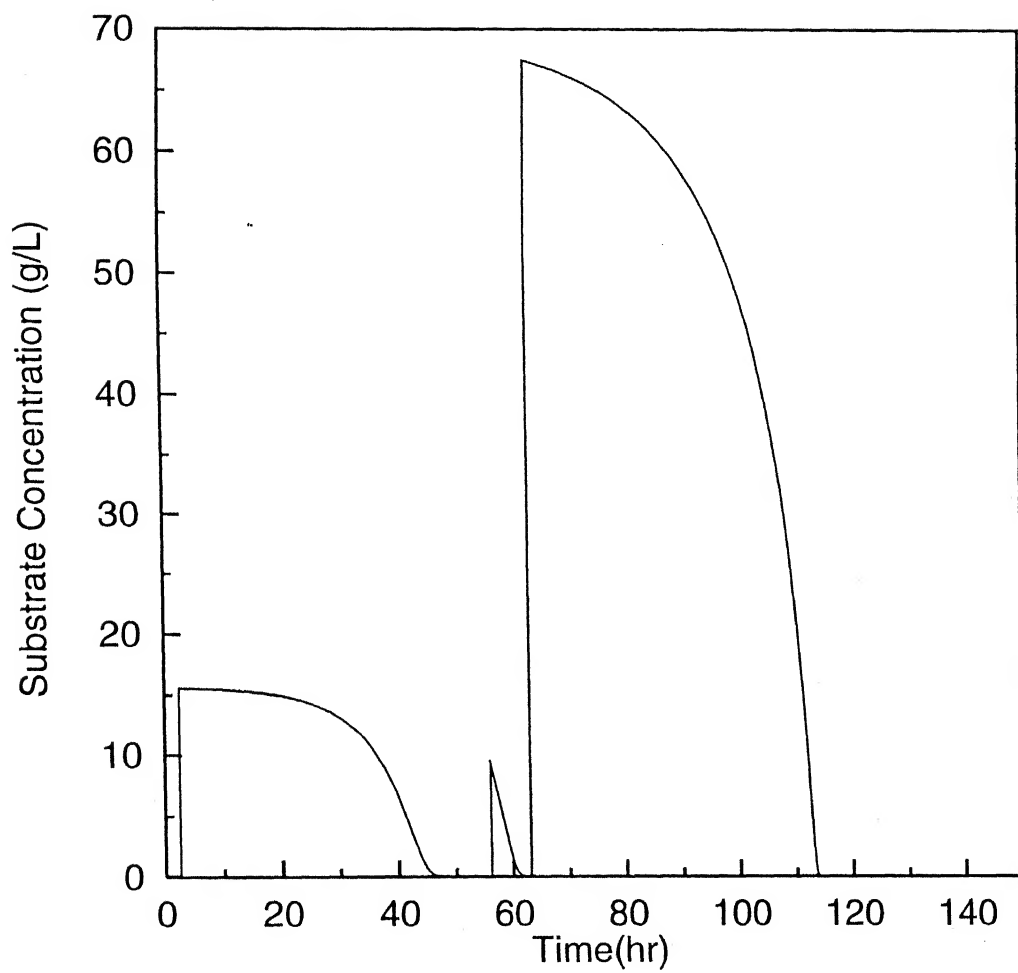


Fig. 4b(ii) : Substrate concentration profile for the free and t_f with unequal intervals.